Support for the present amendments and new claims can be found throughout the specification and claims as filed. For example, support for the amendment to claim 58 can be found, *e.g.*, at page 19, lines 9-10, and at page 1, lines 12-13 and 33-34 of the specification. Support for the amendment to claims 73 and new claim 75 can be found, *e.g.* at page 119, lines 32-34, and page 124, lines 20-22, of the specification. Support for new claim 74 can be found, *e.g.*, at page 118, lines 6-14 of the specification. No new matter has been added.

Rejection under 35 U.S.C. §101:

In the Office Action dated April 3, 2001, the Examiner rejected claims 45, 46, 58, 59, 62, 68, and 70-73 under 35 U.S.C. § 101 for allegedly lacking utility. Specifically, the Examiner asserted that the only cited utilities of the protein encompassed by the present claims that are provided in the specification are to detect the protein, to make antibodies, and to screen drugs, and that while these utilities are credible, they are allegedly neither specific nor substantial (see, pages 2-3 of the Office Action). Applicants respectfully traverse this rejection.

Applicants maintain that the utilities the Examiner acknowledges to be credible in the Office Action are also specific and substantial. In particular, in view of the strong association between the genomic region encoding the present protein and schizophrenia, and in view of the fact that the protein is a novel member of a family of proteins frequently implicated in neuropsychiatric disorders, Applicants submit that the present proteins have specific and substantial utility in the treatment and diagnosis of neuropsychiatric disorders such as schizophrenia.

As described in the specification, the present protein was identified based on its presence in a genomic region that is strongly associated with schizophrenia. The Applicants narrowed down a region previously linked to schizophrenia from a prohibitively large size of about 20 Mb to a size of about 2 Mb, allowing the characterization of this region and the ultimate identification of the present protein. Because genetic associations imply causation, the fact that the gene encoding the present protein is closely flanked by biallelic markers associated with

schizophrenia provides compelling evidence that the G713 protein plays a causative role in the development of or in susceptibility to schizophrenia. Accordingly, on this basis alone, the present protein (*e.g.* when used in detection assays or in screens for modulators), has patentable utility for the treatment or prevention of schizophrenia.

In addition, as described in the specification, the presence of polyglutamine repeats in G713 indicates that this protein is a novel member of a family that has been implicated in a variety of neuropsychiatric disorders, including Huntington's disease (HD), spinobulbar muscular atrophy (SBMA), dentatorubral-pallidolusyan atrophy (DRPLA), and five spinocerebellar ataxias (SCAs 1, 2, 6, 7, and SCA3/MJD). Each of these diseases is caused by an expansion in the number of polyglutamine repeats within the protein members of this family. Further, in many cases, the number of glutamines present in a poly-glutamine repeat within the protein is correlated with decreasing age of onset of symptoms. This molecular feature can thus explain the phenomenon of anticipation, which refers to the tendency for the disease to manifest at an earlier age in successive generations. Schizophrenia has been shown to involve anticipation, and in fact certain publications had speculated that trinucleotide repeat-containing genes would play a role in the etiology of schizophrenia for precisely this reason. For example, Bassett and Honer (*Am. J. Hum. Genet.* 54:864-870; enclosed as Exhibit A) concluded in 1994:

> The results indicate that anticipation is present in familial schizophrenia. These findings support both an active search for unstable trinucleotide repeat sequences in schizophrenia and reconsideration of the genetic model used for linkage studies in this disorder. (*See*, Bassett and Honer, page 1).

Accordingly, the present invention represents an important breakthrough in schizophrenia research, in that it satisfies this long-standing search for a trinucleotide repeat-encoded protein playing a role in schizophrenia.

In view of the direct link between the number of polyglutamine-repeats within members of this protein family and the severity or age-of-onset of various neuropsychiatric disorders, and in view of the association between the immediate genomic vicinity of the gene encoding the

present protein and schizophrenia, the present protein has clear utility for the diagnosis of schizophrenia in an individual, or for a determination in an individual of his or her susceptibility to or likely age-of-onset of the disease. For example, a Western blot can be performed on a biological sample of a patient to determine the relative size of the polyglutamine repeat in the patient's cells, where a relatively large protein would indicate the presence of an abnormally high number of glutamine residues, indicating for example the presence of the disease, of a susceptibility for the disease, or of a likely earlier age-of-onset of the disease. Accordingly, the G713 protein can be used, *e.g.* to make antibodies that specifically recognize the protein and which can thus be used in immunoassays. Applicants note in this regard that, as amended, the present claims are directed to G713 polypeptides, and methods of detecting the same, comprising a glutamine-repeat region.

In view of all of the above, as well as the arguments already of record, Applicants respectfully submit that the present claims clearly satisfy the utility requirement under 35 U.S.C. §101, and thus request withdrawal of the rejection of the present claims under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph:

Claims 45, 46 and 58 to 73 were rejected under 35 U.S.C. §112, first paragraph, for allegedly lacking written description, because the previously pending claims were drawn to a large genus of proteins that was allegedly not adequately described in the specification

In order to expedite prosecution, and without prejudice to future prosecution, Applicants have amended the present claims to read upon G713 polypeptides comprising a glutamine repeat region. Applicants submit that these claims are clearly described in the present specification, and thus respectfully request withdrawal of the rejection of these claims under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §§102(b)/103(a):

Claims 45, 46 , 58, 59, 62, 68, and 70-73 were rejected under 35 U.S.C. §102(b) or §103(a) over Hanson *et al.* ("Hanson") which discloses a 50kD protein present in neuronal cells. According to the Examiner, because Hanson teaches two features of the present protein (i.e. a

molecular weight of 50 kD and a presence in neurons), and is silent regarding a third (i.e; the amino acid sequence), which is an inherent feature, the burden allegedly shifts to the Applicant to demonstrate that the present protein is not the same as that described by Hanson.

As discussed in the Amendment mailed on March 8, 2001, and as discussed during the interview of June 21, 2001, case law and the MPEP explicitly cite that inherency can ***only*** be used to support a rejection under §§102/103 when the allegedly inherent feature is ***necessarily*** present in the cited prior art. A mere possibility that a feature may be present in the art cannot be used to support a rejection on the basis of inherency.

As stated in the M.P.E.P at §2112:

> The fact that a certain result or characteristic ***may*** occur or be present in the prior art ***is not sufficient*** to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)(emphasis added);
>
> "'To establish inherency, the extrinsic evidence `must make clear that the missing descriptive matter ***is necessarily present*** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. ***The mere fact that a certain thing may result from a given set of circumstances is not sufficient***.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)(citations omitted; emphasis added).

In the present case, therefore, until the Examiner has demonstrated that the protein described by Hanson ***necessarily*** has the sequence shown as SEQ ID NO:5, then a *prima facie* case has not been made. The mere fact that Hanson is silent with respect to the amino acid sequence of the detected protein does not in any way demonstrate that the detected protein has the same amino acid as the present protein. Indeed, Applicants have provided evidence that ***multiple distinct proteins*** having a molecular weight of 50 kD are present in neuronal cells (see, *e.g.* Cimato *et al.*, *J Cell Biol* 138:1089-1103 (1997); enclosed herewith as Exhibit B). Further evidence is provided by Applicants enclosed herewith, namely human cypin (Firestein *et al.*, *Neuron* 24:659-72 (1999), enclosed herewith as Exhibit C), human presenilin 2 (De Strooper *et al.*, *J Biol Chem* 272:3590-98 (1997) enclosed herewith as Exhibit D), human protein tyrosine

phosphatase PTP20 (Aoki *et al.*, *J Biol Chem* 271:29422-6 (1996), enclosed herewith as Exhibit E), and human PACSIN 2 (Wasiak *et al.*, *J Biol Chem* 276:26622-8 (2001), enclosed herewith as Exhibit F). In view of the presence of multiple proteins having a molecular weight of 50 kD in neuronal cells, the Examiner has not satisfied the requirements specified in M.P.E.P at §2112 that a rejection based on inherency must be based on a feature that is "necessarily present" in the item described in the art. Accordingly, Applicants submit that the rejection of the present claims over Hanson is improper and should be withdrawn.

Furthermore, Applicants note that an additional limitation of a glutamine repeat has been added to claims. As Hanson does not teach nor suggest a glutamine repeat, the rejection has been overcome and withdrawal of the rejection is respectfully requested.

Power of Attorney

Finally, Applicants wish to comment on a Notice Regarding Power of Attorney mailed on June 26, 2001, to the undersigned Knobbe, Martens, Olson and Bear. The notice stated that, in response to a Power of Attorney filed June 21, 2001, the Power of Attorney to Knobbe, Martens, Olson and Bear has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Applicants submit that the Power of Attorney filed June 21, 2001, was filed merely to add attorneys and agents and did not revoke the Power of Attorney previously granted to Knobbe, Martens, Olson and Bear in this application. Applicants respectfully request confirmation that the Power of Attorney to Knobbe, Martens, Olson and Bear in this application has not, in fact, been revoked and the notice was mailed in error.

Conclusion

In view of the foregoing, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of the rejections is respectfully requested. Should the Examiner have any questions regarding this matter he is invited to telephone the undersigned so that the questions may be resolved.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,
KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 31, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

58. (Twice amended) An isolated, purified, or recombinant glutamine repeat containing polypeptide comprising the amino acid sequence of SEQ ID NO:5.

62. (Amended) An isolated, purified, or recombinant glutamine repeat containing polypeptide, wherein said polypeptide is encoded by the by the nucleotide sequence of SEQ ID NO:4.

73. (Twice amended) A method of ~~determining whether~~ detecting a G713 gene product ~~is present or absent~~ in a biological sample comprising the steps of:

a) obtaining said biological sample from an individual,

b) contacting said biological sample with an antibody that specifically binds the polypeptide of claim 58; and ~~the anti-G713 antibody of any one of claims 46, 70 or 71~~,

c) ~~determining the presence or absence of~~ detecting said G713 gene product in said biological sample.